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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/786,998	PACCIARINI ET AL.	
	Examiner	Art Unit	
	GANAPATHY KRISHNAN	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2012 (RCE)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *18,20-23,26,27,29,30 and 34-42* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *18,20-23,26,27,29,30 and 34-42* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/09/12*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

A Request for Continued Examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 09 November 2012 has been entered.

The Request for Continued Examination filed 09 November 2012 has been carefully considered. The following information has been made of record in the RCE filed for the instant application:

1. Claims 1-17, 19, 24, 25, 28, 31-33 have been canceled. Claims 1-17 and 24 were cancelled in the amendment filed 08/09/2010. Claims 25, 28 and 31-33 were cancelled in the amendment filed 10/24/2011.

2. No new claims have been added in the instant filing. Claims 38-42 were added as new claims in the amendment filed 10/24/2011. The status of claims 38-42 is incorrect.

3. Claim 18 was amended in the amendment filed 10/24/2012.

4. Remarks drawn to rejections under 35 USC 103(a).

Claims 18, 20-23, 26, 27, 29, 30 and 34-42 are pending in the case.

The following are new ground(s) or modified rejections necessitated by Applicant's RCE filed 11/09/12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18, 20-23, 26, 27, 29, 30 and 34-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bargiotti et al (US 5,304,687 of record) in view of Kuhl et al (Cancer Chemother. Pharmacol., 1993, 33, 10-16, of record) in view of Nakamura et al (Gan. To Kagaku Ryoho 1988, Aug. 15 (8 Pt 2), 2562-7, English Abstract, of record) and further in view of Gorbunova (Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver, 1990, of record) and Brem et al (US 5,626,862, of record).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Bargiotti et al, drawn to morpholino derivatives of anthracyclines teach methoxy morpholino doxorubicin (col. 1, lines 10-62; compounds A4 and A5; MMDX-the active agent recited in the instant claims). These derivatives are shown to inhibit solid tumors (part of the limitations of claims 20-22, 31, 32 and new claim 40) such as human carcinoma on administration via intravenous and oral route (col. 11, lines 62-68; col. 12, Table 6). However, the intrahepatic route of administration is not specifically taught (claims 18, 23, 26, 31, 32 and 40 herein).

Kuhl, drawn to doxorubicin derivatives, teaches that the methoxymorpholino derivative of doxorubicin has a broad-spectrum antitumor activity and is non-cross-resistant in multi-drug tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent (Abstract, page 10).

Nakamura et al teach that intra-arterial infusion of lipiodol (iodized oil) and Adriamycin (same as doxorubicin) showed remarkable therapeutic effects in patients with primary and metastatic liver cancer (English abstract). Even though Nakamura has used Adriamycin (Adriamycin is the trade name for doxorubicin) as the active agent it can be seen from the structural formula that doxorubicin (Adriamycin) has an NH_2 attached to the sugar ring whereas methoxymorpholino doxorubicin has the morpholino group at the same position. Since methoxymorpholino doxorubicin (MMDX) is structurally very close to Adriamycin and is known to be active against tumor cell lines one of ordinary skill in the art would use

methoxymorpholino doxorubicin either alone or in combination with lipiodol for the treatment of liver cancer (Board Decision, page 9, line 24 through page 10, line 3).

Gorbunova teaches in general that intra hepatic arterial infusion chemotherapy (limitations of claims 18, 23, 26, 31, 32 and new claim 40 herein) allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor (English abstract). This tells one of ordinary skill in the art that methoxymorpholino doxorubicin can be used in a method of treating liver cancer/tumor via intrahepatic arterial infusion (part of the limitations of claims 18, 20-22, 25, 26, 31-32, and new claim 40). This is obvious from the teaching of Bargiotti and Kuhl. Moreover, methoxymorpholino derivative of doxorubicin (MMDX) is activated in the liver to a metabolite that is ten times more potent (according to Kuhl; Board Decision, page 12, line 24 through page 13, line 4).

Brem et al. teach delivery of chemotherapeutic agents for treating tumors in general. According to Brem et al. pulse or short term infusions of chemotherapeutic agents are better than continuous infusions (col. 1, lines 38-42; limitations with respect to duration of administration of active agent recited in claims 18-19, 25, 31-33 and new claims 38, 39). Adriamycin, which is closely related to MMDX, has been suggested for administration for a period of at least a month (col. 7, line 65 and col. 8, lines 24-25). Even though this is with respect to Glioma this teaching of short term infusions and the duration of administration can be applied to the treatment of liver tumors and cancers using MMDX as the active agent. The time period for short term infusion and frequency can be optimized for maximum beneficial effects and is well within the skill level of the artisan.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising methoxymorpholino doxorubicin with iodized oil and use the same in a method of treating a human liver tumor/cancer and reducing systemic exposure as instantly claimed since such is seen to be taught in the prior art. It is well within the skill level of one of ordinary skill in the art to adjust dosages and the frequency of administration (claims 18-19, 25, 28-30, 31-36 and new claims 40-42 herein) based on the dosages taught in the prior art in order to obtain optimal beneficial effects.

MPEP 2141 states, "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusatory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) " Obvious to try " choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on

design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention." According to the rationale discussed in KSR above, the rationale in (A) and (C) above are seen to be applicable here since based on the prior art teachings:

(a) Nakamura discloses a composition for treating liver cancer comprising doxorubicin and lipiodol, which is an agent that remains in the tumor after injection through the hepatic artery.

(b) Kuhl discloses that MMDX, a methoxymorpholino derivative of doxorubicin, has a "broad spectrum of preclinical activity. Although Kuhl relates to leukemia and lymphoma, Bargiotti discloses that MMDX has been shown to inhibit solid tumors. This makes it obvious to form a composition comprising MMDX and lipiodol. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. The use of the resulting composition for treating liver cancer is also obvious (Board Decision, page 9, lines 17-22).

(c) Intrahepatic arterial administration produces a high concentration of the active agent in liver according to Gorbunova. It is obvious to treat liver cancer by intrahepatic administration of MMDX-lipiodol composition. This would also reduce systemic exposure (Board Decision, page 9, line 23 through page 10 line 3; page 16, lines 4-14).

Thus, it is obvious to combine prior art elements and improve the method of the prior art to yield predictable results by administering MMDX in combination with iodized oil via intrahepatic arterial administration in a method treating liver tumor/cancer and in a method reducing systemic exposure of MMDX. Since administration of MMDX is via intrahepatic artery produces a high concentration of its metabolite in the liver directly, systemic exposure is reduced (Board Decision, page 14, line 4 through page 17).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art. Method improvement is the motivation.

Response to Applicants Arguments

Applicants have traversed the rejection above of record arguing that:

The claims are drawn to a method of treating liver cancer using MMDX as the active agent. None of the references teach the use of MMDX for liver cancer. The supposition that MMDX would be potentiated in the liver and therefore would have been thought effective for liver cancer treatment is flawed. It presupposes a healthy liver. A cancerous liver is not a healthy liver. At the time of filing the artisan knew that the liver microsome P-450 was the one principally involved in drug metabolism. According to the Hamamoto et al reference (and others cited by applicant in exhibit A) cytochrome P-450 in a liver is converted to cytochrome P-420 9in active form) and the specific activities were reduced compared to those in the normal liver. It is known that MMDX is potentiated in the liver but if the liver is cancerous the potentiation is

not possible. With this state of art the fact that MMDX is effective at all and more saliently, at the low dosage claimed, is unexpected and non-obvious.

Applicants' arguments and the references cited in Appendix A have been considered but are not found to be persuasive.

Kuhl, drawn to doxorubicin derivatives, teaches that the methoxymorpholino derivative of doxorubicin has a broad-spectrum antitumor activity and is non-cross-resistant in multi-drug tumor resistant models. It is also activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent (Abstract, page 10). This tells one of ordinary skill in the art that since the metabolite of MMDX is ten times more potent a lower dosage level can be administered. The artisan would definitely use lower dosage levels because of this teaching of the prior art regarding the MMDX, which is also the instant active agent. Gorbunova teaches in general that intra hepatic arterial infusion chemotherapy allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor (English abstract). This tells one of ordinary skill in the art that methoxymorpholino doxorubicin can be used in a method of treating liver cancer/tumor via intrahepatic arterial infusion.

Hamamoto et al teaches that the amount of cytochrome P-450 is lower in a cancerous liver tissue compared to a normal tissue (page 8, Table 1 and left col. lines 1-5). Since cytochrome P-450 is the potentiating agent and it is also known that MMDX is converted into its metabolite that is ten times more active, one of ordinary skill in the art will recognize that the lower amount of cytochrome P-450 present in the cancerous liver can still metabolize MMDX. Even though the concentration of the metabolite will be lower, because it is ten times more

potent it can still express its anticancer activity in the liver. It would be a problem only if cytochrome P-450 is totally absent. According to Hamamoto et al it is not completely converted to P-420.

The Mouelhi et al reference discloses that the drug-metabolizing enzymes are decreased in primary hepatic malignancies and arylsulfatase is the one which is markedly reduced, not P-450 (page 464, line 3 under Discussion). Mouelhi et al also discloses that comparison of experimental hepatocarcinogenesis with liver tumors in humans is very difficult and extrapolation of data from laboratory animals must entail caution (page 464, right col., last paragraph). The Lau et al reference teaches that MMDX is believed to be metabolized by cytochrome P-450 IIIA isoform (page 83, right col., lines 1-6).

Based on the art cited by applicants it was not established at the time of invention that cytochrome P-450 is completely converted to the inactive for P-420 and also if it is the enzyme involved in drug metabolism. One of ordinary skill in the art therefore will not be dissuaded from using MMDX in the treatment of liver cancer as instantly claimed because of the above teachings regarding the enzymes that metabolize the drugs. The observation by applicants that MMDX is effective at the low dosage claimed is still rendered obvious by the prior art of record since the claims are drawn to treating liver cancer and such an effect at lower dosage using MMDX is rendered obvious.

Conclusion

Claims 18, 20-23, 26, 27, 29, 30 and 34-42 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 9.00am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ganapathy Krishnan/
Examiner, Art Unit 1623.